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(54) **A method of hormonal treatment of peri-menopausal, menopausal and post-menopausal disorders and multi-preparation pack therefor**

Verfahren zur hormonalen Behandlung von Störungen in der Peri-Menopause, Menopause und Post-Menopause und Verpackung mit multiplen Präparaten dafür

Méthode de traitement hormonal de troubles de la périménopause, ménopause et postménopause et emballage à préparations multiples dans ce but

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(73) Proprietors:  
• **PRE JAY HOLDINGS LTD.**  
Mississauga, Ontario L5J 4E3 (CA)  
• **WOCO INVESTMENTS LTD.**  
London, Ontario N6G 1R2 (CA)

(72) Inventors:  
• **Plunkett, Earl Robert**  
London, ON, N6H 4C4 (CA)  
• **Wolfe, Bernard Martin Joseph**  
London, ON, N6G 1R2 (CA)

(74) Representative: Lawrence, Peter Robin  
Broughton et al  
**GILL JENNINGS & EVERY,**  
Broadgate House,  
7 Eldon Street  
London EC2M 7LH (GB)

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**EP 0 136 011 B1**

## Description

This invention relates to products for hormonal treatment for menopausal (including perimenopausal and post-menopausal) disorders in women, and particularly for a treatment involving the continuous administration of a progestogen in conjunction with an estrogen. The invention further relates to a pharmaceutical composition comprising selected dosage units of progestogen and estrogen. In another aspect, the invention is concerned with a regimen comprising the continuous administration of progestogen in conjunction with the cyclical administration of estrogen and to a multi-preparation pack containing selected dosage units of progestogen and estrogen and particularly adapted to such regimen.

Perimenopausal (i.e. over approximately forty years of age), menopausal and post-menopausal women frequently experience a large variety of conditions and disorders which have been attributed to estrogen deprivation due to ovarian failure. The duration of these disorders can be extremely variable, and include hot flushes which can be devastating in some women and very mild in others. Dryness of the vagina associated with susceptibility to minor infections, and frequently associated with discomfort during intercourse, is another symptom which may be directly related to the decrease in estrogen availability.

In a long-term sense, one of the most health-threatening aspects of the menopause is the loss of mineral from bone (osteoporosis) which produces a decrease in bone mass and generates a serious risk of fractures. For example, evidence exists that there is a six-fold increase in fractures in post-menopausal women as opposed to men of the same age (Garraway et al, Mayo Clinic Proceedings, 54, 701-707, 1979). These fractures, of course, carry a high complication rate among older people, a marked increase in disability and general morbidity, and certainly an increased risk of mortality.

Another serious health-threatening aspect of the menopause is the impressive loss of protection against heart attacks which is enjoyed by younger women up to the age of 60, when compared to men of the same age. The steep increase in mean serum cholesterol concentration which occurs around the menopause (during the fourth and fifth decades) may contribute importantly to the progressive increase in death from ischemic heart disease in older women. In the eighth and ninth decades, the incidence of deaths from ischemic heart disease approaches that of men (Havlik, R.J. and Manning-Feinleid, P.H. 1979, NIH Publication No. 79-1610, U.S. Department of HEW).

In addition to the above-mentioned major physical problems, some women experience a larger variety of other symptoms ranging from depression, insomnia, and nervousness, to symptoms of arthritis and so forth.

It is generally agreed that estrogen is the most effective agent for the control or prevention of menopausal flushes and vaginal atrophy. It is effective in retarding or preventing the appearance of clinical evidence of osteoporosis. In appropriate doses, when combined with di-norgestrel (or laevo-norgestrel), a favourable effect upon blood lipids is also seen. Problems with estrogen therapy do exist, however, and have been widely explored and documented in the medical literature. The means by which estrogen has been administered, generally speaking, involves either the use of estrogen alone or estrogen plus a progestogen.

Estrogen alone, given in small doses on a continuous basis, is effective in most patients for the control of the above symptoms and problems associated therewith. However, although the vast majority of women taking continuous low-dose estrogen will not have bleeding for many months or even years, there is a distinct risk posed by this routine of silently (i.e. exhibiting no overt symptoms) developing "hyperplasia of the endometrium". This term refers, of course, to an overstimulation of the lining of the uterus which can become premalignant, coupled with the possibility that the patient will eventually develop cancer of the uterine lining even under such a low-dose regimen (Gusberg et al, Obstetrics and Gynaecology, 17, 397-412, 1961).

Estrogen alone can also be given in cycles, usually 21-25 days on treatment and 5-7 days off treatment. Again, if small doses of estrogen are required to control the symptoms and it is used in this fashion, only about 10% of women will experience withdrawal bleeding between the cycles of actual treatment. However, one must again be concerned by the risk of developing endometrial hyperplasia and by the increased relative risk of developing cancer of the uterus (Research on the Menopause: Report of a W.H.O. Scientific Group, 53-68, 1981).

The addition of progestogen for the last 7-10 days of each estrogen cycle will virtually eliminate the concern about developing endometrial hyperplasia and probably reduce the risk of developing endometrial carcinoma below that of the untreated general population. However, withdrawal bleeding will occur regularly in this routine and this is highly unacceptable to most older women (Whitehead, Am. J. Obs/Gyn., 142, 6, 791-795, 1982).

One example is described in GB-A-2096462, which relates to a product for the treatment of menopausal symptoms in which the product is administered in a multi-phase sequence comprising administering estrogen alone, followed by administering estrogen and progestogen, followed by a phase where neither estrogen nor progestogen is administered.

Still another routine for estrogen administration would involve a formulation such as those found in birth control pills which contain relatively small doses of estrogen over the full 20-21 day treatment cycle, plus very substantial doses of potent progestogens over the same period of time. This routine, of course, not only produces withdrawal bleeding on each cycle, but is further unacceptable because such formulations have been shown to carry an increased risk of developing arterial complications such as stroke or myocardial infarction in older women about the age of 35-40. This is

especially true if the individual is a smoker of cigarettes (Plunkett, Am. J. Obs/Gyn. 142, 6, 747-751, 1982).

Therapeutic regimens employing a progestogen alone require relatively large doses in order to control hot flushes. Moreover, use of a progestogen alone does not prevent atrophy of the vaginal mucosa, although it may help to prevent osteoporosis. However, a progestogen administered in large doses, together with large amounts of a synthetic estrogen, induces changes in blood lipids which may promote arteriosclerotic changes and have been implicated in the appearance of strokes and myocardial infarction among women taking oral contraceptives in their later reproductive years, (Plunkett, supra).

Treatment of menopausal symptoms is also described in Acta Obstet Gynecol Scand 59, page 327-329 (1980), where a pilot study was carried out using different treatments comprising administering estradiol valerate and norgestrel or norethisterone acetate. Generally the regimens described contain high levels of progestogen. One regimen described is the continuous administration of 2mg estradiol valerate and 1mg norethisterone acetate, daily. However, it is explained that for this particular combination, the continuous regimen is unacceptable clinically due to irregular spotting.

The present invention provides a novel therapeutic method and product involving the use of low dosage levels of estrogens and progestogens, which method is designed to avoid or minimize bleeding and prevent overstimulation of the lining of the uterus while producing favourable changes in blood lipids. In particular, the method involves continuous and uninterrupted administration of very small doses of a progestogen along with administration of an estrogen, the latter being cyclical, where required (for example, with perimenopausal women). The method specifically provides for treatment of menopausal or post-menopausal disorders in a woman comprising either:

- A. continuously and uninterruptedly administering a progestogen and an estrogen to said woman, or
- B. continuously and uninterruptedly administering a progestogen and cyclically administering an estrogen to said woman by repetitively using a dosage regimen comprising:

- (i) administering said estrogen continuously for a period of time between about 20 and about 120 days, followed by
- (ii) terminating administering said estrogen for a period of time between about 3 and about 7 days.

The term "perimenopausal" refers to women of approximately forty years of age and older, who have not yet definitely arrived at menopause but who are experiencing symptoms associated with menopause.

The term "continuous" as applied in the specification and the claims to "administration" means that the frequency of administration is at least once daily. Thus, administration, e.g. every other day or once every third day, is not "continuous" for purposes of this invention. Note, however, that the frequency of administration may be greater than once daily and still be "continuous", e.g. twice or even three times daily so long as the dosage level as specified herein is not exceeded.

The term "uninterrupted" means that there is no break in the treatment. Thus "continuous, uninterrupted administration" of a progestogen would mean that the progestogen is administered at least once daily essentially in perpetuity or until the entire treatment is ended. In this regard, it should be noted that "cyclical" administration means that there is a break in administration and that, therefore, by definition, cyclical administration cannot be "uninterrupted".

The term "dosage level" means the total amount of estrogen or progestogen administered per day. Thus, for example, the "continuous administration" of a progestogen to a woman at a "dosage level" of 75 micrograms means that the woman receives a total of 75 micrograms of progestogen on a daily basis, whether the progestogen is administered as a single 75 microgram dose or, e.g. three separate 25 microgram doses. It is noted that the most conventional means of continuously administering an estrogen or progestogen is as a single daily oral dose at the prescribed dosage level. Parenteral modes of administration, which provide a slow release of the progestogen, could be substituted for the oral route.

Thus, the invention realizes the objects of providing a therapeutic method allowing for the administration of an estrogen, controlling hot flushes, restoring the vaginal mucosa to a healthier state, preventing the development of the demineralization of bones as well as preventing changes in lipids which predispose to cardiovascular disease, over long periods of treatment, which method does not, however, initiate bleeding or increase the risk of endometrial carcinoma.

In another aspect, the invention provides a pharmaceutical product for hormonal treatment of menopausal or post-menopausal disorders in a woman, which comprises a dosage unit of a progestogen and a dosage unit of an estrogen in which progestogen is to be administered continuously and uninterruptedly in a daily dosage equivalent to orally administered laevo-norgestrel in an amount of from 0.025 to 0.075mg and estrogen is to be administered uninterruptedly in a daily dosage equivalent to orally administered estradiol in an amount of from 0.5mg to 2.0mg with the proviso that where estradiol valerate and norethisterone acetate are to be administered, the maximum daily dosage of said estradiol valerate is equivalent to orally administered estradiol in an amount of 1.0mg.

The actual unit dosages are selected according to conventionally known methods, e.g. body weight of patient and biological activity of the hormones, with the ultimate goal of producing the desired result with the minimum quantities of

hormones.

The interruption of the estrogen administration is required in perimenopausal women to maintain normal periods and may be required in certain jurisdictions due to health concerns - particularly overstimulation of the lining of the uterus to cause a pre-malignant condition. The absence of estrogen for a short period allows the lining of the uterus to be sloughed and any pre-malignancy thus avoided. However, the inventors believe that even with continuous administration of estrogen, the presence of progestogen will give rise to sufficient atrophy of the uterus that no such condition would be likely to occur.

This invention also provides a product comprising, in combination, progestogen and estrogen in a form in which progestogen is to be administered uninterruptedly in a daily dosage equivalent to orally administered laevo-norgestrel in an amount of from 0.025mg to 0.075mg and estrogen is to be administered by cyclical administration in an amount in a daily dosage equivalent to orally administered estradiol in an amount of from 0.5mg up to 2.0mg.

A further and important object of the invention is to provide the means whereby a woman may receive the proper quantities and dosage units of the progestogen and estrogen for adherence to the prescribed regimen wherein the dosage of estrogen is cyclically administered. Such means generally takes the form of a multi-preparation pack, which facilitates administration by a nurse or physician in appropriate circumstances or, more usually, self-administration by the woman.

The multi-preparation pack contains sufficient dosage units of progestogen and estrogen for continuous administration of both said progestogen and said estrogen for a period of from about 20 to 120 days optionally plus an additional number of dosage units of progestogen for administration for an additional period of time of from about 3 to about 7 days during which administration of said estrogen is terminated. Preferably the estrogen is administered for a period in the range 30 to 120 days.

A preferred product comprises one or more unit dosages of a composition containing an estrogen and a progestogen with a suitable pharmaceutically inert carrier in which the progestogen is administered in a daily dosage equivalent to up to 0.050mg orally administered laevo-norgestrel and the estrogen is administered in daily dosage equivalent to orally administered estradiol in an amount of up to 1.0mg. Preferably the product is in the form of a multi-preparation pack comprising a plurality of these unit dosages.

The product may alternatively be in the form of a parenteral slow release composition comprising an estrogen and a progestogen, usually in the form of an implant or an intramuscular depot, which releases dosages equivalent to orally administered daily dosages of estrogen of up to 2.0mg estradiol, preferably 0.5 to 2.0 mg and of progestogen up to 0.075mg laevo-norgestrel, preferably 0.025mg to 0.075mg.

The invention also includes a product comprising in combination, progestogen and estrogen in which progestogen is to be administered uninterruptedly in a daily dosage equivalent to orally administered laevo-norgestrel in an amount up to 0.075mg and estrogen is to be administered either uninterruptedly or cyclically in an amount in a daily dosage equivalent to orally administered estradiol in an amount up to 2.0mg and at least the progestogen is in the form of a slow release composition suitable for implanting or injecting intramuscularly.

One type of product for use in the treatment of menopausal disorders by the continuous and uninterrupted administration of a progestogen in conjunction with the administration of an estrogen therefore comprises unit dosages of estrogen in a daily dosage equivalent to orally administered estradiol in an amount up to 2.0mg and unit dosages of progestogen in a daily dosage equivalent to orally administered laevo-norgestrel in an amount up to 0.075mg, preferably together in a single container. Usually this type of product comprises a multi-preparation pack comprising unit dosages of estrogen sufficient for a period of treatment of 20 to 120 days, preferably 30 to 120 days, and unit dosages of progestogen sufficient for at least the same period of treatment and preferably for an additional period of treatment of 3 to 7 days. The product is formulated to permit administration separately or simultaneously of the unit dosages of estrogen and progestogen. The dosages may contain one only or both of estrogen and progestogen. During periods of treatment when both hormones are to be administered the dosages of estrogen and progestogen may be taken simultaneously or separately, but are preferably taken simultaneously and usually both hormones will be contained in the same unit dosage in the form of, for example, a pill, capsule or tablet.

The estrogens used in the present disclosure may be those which are orally active and are suitable for oral contraception and selected from natural estrogens such as estradiol, estradiol 17-beta, estradiol valerate, conjugated equine estrogens, piperazine estrone sulphate, estrone, estriol, estriol succinate and polyestriol phosphate, or from synthetic estrogens such as ethinyl estradiol, quinestranol and mestranol. The natural estrogens are preferred.

The progestogen is again selected from those which are orally active and suitable for oral contraceptives and may be, for example, dl-norgestrel, laevo-norgestrel, norethindrone (norethisterone), norethindrone acetate, ethynodiol diacetate, medroxyprogesterone acetate, cyproterone acetate, norethynodrel, dydrogesterone, allylestrenol, quingestanol acetate, lynoestrenol, medrogestone, norgestrienone, dimethisterone and ethisterone.

In the following Tables IA and IB are listed preferred unit dosages, minimum unit dosages and maximum unit dosages for the estrogens and progestogens useful in this invention. The quantities are determined by the biological activities of the particular substances as obtained commercially from sources that normally supply them in micronised form.

TABLE 1A

ESTROGENS			
Natural estrogens (steroids)	Preferred	Dosage (mg/day)	
		Minimum	Maximum
Estradiol	1	0.500	2
Estradiol-17 $\beta$	1	0.500	2
Estradiol valerate	1	0.500	2
Conjugated equine estrogens	0.600	0.300	2.5
Estrone	0.600	0.300	2.5
Piperazine estrone sulphate (estropipate)	0.500	0.250	2.5
Estril*	0.100	0.050	0.500
Estril succinate*	0.100	0.050	0.500
Polyestriol phosphate*	0.100	0.050	0.500
Synthetic estrogens (steroids)			
Ethinyl estradiol	0.010	0.005	0.020
Mestranol	0.015	0.005	0.040
Quinestranol	0.010	0.005	0.030

It may be noted that of the estrogens of Table 1A, the estril preparations marked with an asterisk (\*) have lower preference than estradiols or estrones because they fail to spare bone in post-menopausal women. However, they could be combined with natural or synthetic estrogens for the purpose of the invention. Also, it is preferable that the following non-steroidal estrogens - although useful in this invention - be avoided for women who have not definitely arrived at menopause (who could become pregnant) - estrogens of this type being known to induce vaginal cancer and other abnormalities in offspring if taken during the pregnancy:

Stilboestrol	0.100	0.020	2
Stilboestrol dipropionate	0.100	0.020	2
Diethylstilboestrol	1	0.400	2.5
Chlorotrianisene	2	1	2.5
Benzoestrol	2	0.5	2.5
Dienoestrol	0.500	0.200	2.5
Hexoestrol	0.500	0.200	2.5
Methallenoestriol	1	0.500	2.5

TABLE 1B

PROGESTOGENS			
	Preferred	Dosage (mg/day)	
		Minimum	Maximum
Laevo-norgestrel	0.050	0.025	0.075
di-norgestrel	0.100	0.050	0.150
Norethindrone (norethisterone)	0.30	0.15	1.0
Norethindrone (norethisterone) acetate	0.20	0.10	1.0
Ethinodiol diacetate	0.30	0.10	1.0
Dydrogesterone	10	5	30
Medroxyprogesterone acetate	2.5	1	15
Norethynodrel	1	0.200	5
Allylestrenol	2	1	10
Lynoestrenol	0.200	0.100	2
Quingestanol acetate	0.200	0.050	1
Medrogestone	2	1	10
Norgestrienone	0.050	0.020	0.200
Dimethisterone	1	0.500	15
Ethisterone	2.5	1	25
Cyproterone acetate	0.500	0.100	10
Chlormadinone acetate	0.300	0.100	1
Megestrol acetate	1	0.100	10

Although chlormadinone acetate and megestrol are useful in the context of this invention, it has been speculated that these progestogens may pre-dispose breast tumors, although no clinical proof exists to that effect. However, unless and until such suspicions are proven to be without foundation, these compounds are clearly of lower preference.

The estrogen/progestogen combinations may be administered non-orally by implants or intramuscular injections. Generally speaking, the required dosages are based upon somewhat lower daily dosage levels than those required for the orally administered estrogens and progestogens, for the simple reason that the former are directly released into the bloodstream with consequently greater activity than the same compounds when orally ingested.

Estradiol, estradiol valerate and estradiol 17- $\beta$  are suitable candidates for estrogen implants, in maximum and minimum amounts of 100 mg and 20 mg, with 100 mg preferred. These quantities will be suitable for slow-release implants intended for replacement every 3 to 12 months.

Suitable progestogen implants and intramuscular injections are set forth in Table 1C.

TABLE 1C

Progestogen implants	Period	Preferred	Total Quantity (mg)	
			Minimum	Maximum
Laevonorgestrel	every 2-5 yr.	50	25	100
dl-norgestrel	every 2-5 yr.	100	50	200
Norgestrienone	every 1-2 yr.	100	25	200
Norethindrone acetate	every 2-4 mon.	100	25	200
Intramuscular progestogen depots				
Medroxyprogesterone acetate	every 3 mon.	150	50	500
Norethindrone enanthate	every 3 mon.	50	20	400
Gestronol hexanoate	every 3 mon.	100	50	400
Algestone acetophenide	monthly	50	20	300
Hydroxyprogesterone hexanoate	weekly	100	50	250
Hydroxyprogesterone caproate	bi-weekly	100	50	250

dl-Norgestrel, laevo norgestrel (the common name for d-13 $\beta$ -ethyl-17 $\alpha$ -ethinyl-17 $\beta$ -hydroxygon-4-en-3-one), norethindrone (common name for 17-hydroxy-19-nor-17 $\alpha$ -pregn-4-en-20-yn-3-one), ethynodiol diacetate (common name for 19-nor-17 $\alpha$ -pregn-4-en-20-yne-3 $\beta$ , 17-diol diacetate), norethindrone acetate, and cyproterone acetate may also be administered by injection. It will be readily appreciated by those skilled in the art that any other synthetic progestogen which is orally active or effective for use in conjunction with contraception is also suitable for use in this invention.

Any of the suitable estrogens and progestogens (particularly those listed in the foregoing tables) may be combined with one another in the quantities recited to give estrogen/progestogen combinations within the purview of the invention. Especially preferred combinations are those containing the estradiols or conjugated equine estrogens and the norgestrels norethindrones, or medroxyprogesterones. Thus, especially preferred combinations are:

Table 1D

	Estradiol/Laevo-norgestrel
5	Estradiol 17 $\beta$ /Laevo-norgestrel
	Estradiol valerate/Laevo-norgestrel
	Conjugated equine estrogens/Laevo-norgestrel
10	Estradiol/dl-norgestrel
	Estradiol 17 $\beta$ /dl-norgestrel
	Estradiol valerate/dl-norgestrel
	Conjugated equine estrogens/dl-norgestrel
15	Estradiol/Norethindrone (norethisterone)
	Estradiol 17 $\beta$ /Norethindrone (norethisterone)
	Estradiol valerate/Norethindrone (norethisterone)
20	Conjugated equine estrogens/Norethindrone (norethisterone)
	Estradiol/Norethindrone (norethisterone) acetate
	Estradiol 17 $\beta$ /Norethindrone (norethisterone) acetate
25	Estradiol valerate/Norethindrone (norethisterone) acetate
	Conjugated equine estrogen/Norethindrone (norethisterone) acetate
	Estradiol/Medroxyprogesterone acetate
	Estradiol 17 $\beta$ /Medroxyprogesterone acetate
30	Estradiol valerate/Medroxyprogesterone acetate
	Conjugated equine estrogen/Medroxyprogesterone acetate

35 The maximum, minimum and preferred dosage levels for the respective estrogens and progestogens in the foregoing combinations are as recited in the tables.

The composition of the invention is usually administered orally in admixture with a pharmaceutically acceptable inert carrier. The estrogen and progestogen can be compounded in any pharmaceutically acceptable inert (non-toxic) form. The packaging can be any system convenient for proper delivery. With the preferred orally administrable form, the pharmaceutical carrier can be any of the conventionally employed carriers, for example pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate, and similar substances. The compositions may be formulated into solutions, suspensions, tablets, pills, capsules, powders, sustained release formulations, etc.

45 One of the unique aspects of this invention is the adaptation of the multi-preparation pack to the continuous uninterrupted administration of a progestogen and an estrogen when estrogen is administered in a cyclic fashion. The duration of the estrogen cycle can be very variable, with continuous administration ranging between 20 and 120 days followed by a break (i.e. interruption) in estrogen administration ranging anywhere from about 3 to about 7 days. However, if the estrogen is discontinued for a period longer than 5 days, recurrence of hot flushes is most likely to occur in a number of patients.

50 The multi-pack dispensing system may be accommodated by conventional packaging equipment, e.g. transparent strip foil packages continuously arranged in daily dosages or other conventional means in the art. Where the multi-pack is employed for the cyclical administration of an estrogen in combination with a progestogen, the pack would conveniently comprise a transparent strip foil package with the combined unit daily dosages arranged continuously with, for example, up to a total of 120 such dosages, the 3 to 7 unit dosages of progestogen being located at the end of the combined daily unit dosages whereby they would be taken at the end of the series.

55 The inventors have developed clinical evidence from this routine that the amounts of estrogen and progestogen required to control flushes, vaginal symptoms and associated subjective symptoms are very small. Preliminary metabolic responses of the subjects indicate favourable changes toward the lower blood lipid levels found in younger premenopausal women.



**EXAMPLE 1**

An experimental study of thirty women was instituted under a randomized double blind protocol with crossover and involved the administration of placebos, progestogen only, estrogen only and the combination of the continuous, uninterrupted progestogen/cyclic estrogen treatment. Treatment comprised administering each hormone and the combination as follows: (1) estrogen alone for two months; (2) progestogen alone for two months; (3) combination therapy using (1) and (2) for six months. Each period of administering a hormone of the combination was followed by a one month period of placebo (substance with no endocrine activity) administration. The estrogen was micronized 17 $\beta$ -estradiol administered at a daily dosage level of 1 milligram, while the progestogen was dl-norgestrel administered at a dosage level of 75 micrograms.

Of 30 women who have completed this study, 22, on the basis of their responses throughout the fourteen months of observation, selected the combination treatment and requested to continue it. This represents a high level of acceptability.

**EXAMPLE 2**

In a follow-up phase of observation, 17 subjects (with intact uterus) have completed a total of 125 lunar months of the combination therapy (continuous, uninterrupted administration of dl-norgestrel, cyclic administration of 17 $\beta$ -estradiol). None of the patients experienced "bleeding" which required protection. 1.6 percent of the cycles involved spotting requiring no protection. 98.4 percent of the cycles were completely clear.

The combination therapy has been associated with no evidence whatsoever of endometrial hyperplasia (overstimulation of the lining of the uterus). One patient, after the 2-month phase of taking estrogen only (in the double blind study) did show evidence not only of hyperplasia of the endometrium but also had atypical findings which could be interpreted as indicative of a premalignant change. Addition of the small (75 microgram) dosage level of progestogen (dl-norgestrel) for two weeks only followed by full dilatation and curettage revealed that the endometrium had become completely atrophic once again and a total reversal of the previous findings were noted.

As an alternative to dl-norgestrel, laevo-norgestrel may be used. Since the dl-norgestrel consists of equal parts of the dextro (inactive) and laevo (active) forms, only half the quantity of laevo-norgestrel is used with the same effect. Thus, if laevo-norgestrel is substituted for dl-norgestrel in the foregoing examples, the laevo-norgestrel dosage level is 37.5 micrograms.

At least five cases of young women who required removal of ovaries and uterus because of severe endometriosis have also been successfully treated by the above combination. These women rarely have total removal of the endometriotic tissue. It is important to treat these patients with estrogen replacement therapy to prevent the early appearance of bone demineralization (osteoporosis), elevation of cholesterol and triglycerides and to control severe hot flushes and vaginal atrophy. If patients such as these are treated with estrogen alone, they frequently develop recurrence of pain symptoms due to residual endometriosis being restimulated by the administered estrogen. Because the inventors' combination therapy tends to promote atrophy of the lining of the uterus (endometrium) no matter whether it is located normally within the uterus or in the endometriotic tissue in the pelvis, it is found that these patients tolerate the treatment very well and do not have a recurrence or reactivation of their endometriosis. Furthermore, even small doses of estrogen in combination with the continuous progestogen routine is sufficient to control the severe hot flushes which such patients experience.

Thus this invention permits control of menopausal disorders including hot flushes and vaginal atrophy along with many of the subjective symptoms. Further, given that both components of the combination therapy are considered to be effective in retarding osteoporosis, long term therapy to prevent this disabling disease should be effective.

Additionally, the risk of developing endometrial (uterine) cancer from the combination therapy should, at a minimum, be reduced to the normal incidence of the general population as opposed to the increased risk which has in fact been demonstrated to occur using estrogen-only treatment. The inventors have in fact developed some evidence suggestive that the combination therapy reduces the risk of premalignant endometrial changes, which may reduce the risk of developing endometrial cancer. The reduction in bleeding or spotting in patients taking the combination therapy makes it much more desirable relative to known treatments, particularly to older women.

The following describes directions which may be applied to a multi-preparation pack specifically adapted to the cyclical administration of estrogen together with the continuous administration of progestogen in accordance with one embodiment of the invention:

**ABOUT THESE TABLETS**

(The tablet set herein) is used to control menopausal symptoms. It is not a birth control pill and cannot be relied upon to prevent pregnancy.

Oral contraceptives should not be taken at the same time as these tablets and, if necessary, you should therefore

ask your doctor about alternative means of mechanical protection.

When treatment is first started, tingling of the breasts slight nausea or occasional vaginal bleeding may occur - this should settle after a short time.

If you have any unusual symptoms, contact your doctor.

To be taken under medical supervision.

#### HOW TO USE THIS PACK

Whether you are menstruating regularly or not, take the first tablet on a day suitable to yourself until all the tablets have been consumed.

**THE LAST SEVEN TABLETS OF THE DIFFERENT COLOUR ARE TO BE TAKEN ONLY WHEN ALL OTHERS HAVE BEEN CONSUMED.**

Alternatively, the foregoing instructions may be printed as a leaflet, and the package instructions modified as follows:

Before commencing treatment please read the enclosed instruction leaflet carefully. If you have any difficulties following the instructions please ask your doctor for assistance.

#### DIRECTIONS

To remove a tablet, press firmly with your thumb on the appropriate clear plastic bubble. This may be helped by holding the card so that your other fingers surround the aluminum foil through which the tablet will emerge.

A multi-preparation pack suitable for administration of tablets in accordance with the regimen described above is illustrated in Figures 1 and 2 of the drawings. A bubble pack 10 (which may be folded along the line 10a) is sold in a protective sleeve 11, upon the rear of which are printed the directions for use and salient facts concerning the tablets, as indicated at 12 in the drawing. When removed from the protective sleeve by the consumer, the bubble pack contains as many tablets as the number of days which the pack is intended to cover (in this example, one hundred and twenty days). Optionally, the individual bubble segments may be numbered from one to one hundred and twenty but it is important that the last few segments, which contain the progestogen-only tablets, be clearly distinguished from the remainder of these segments. In the present example, the segments 13 containing the first one hundred and thirteen tablets (combination progestogen/estrogen) are a light colour (for example, white) whilst the last seven segments 14, containing the progestogen-only tablets are a dark colour (red, for example). By following the directions on the sleeve and observing the colours on the bubble pack (and the "day numbers", if present) the consumer will take the combination tablets for the first one hundred and thirteen days and the progestogen tablets for the last seven days. Thereafter, a new package would be opened, whereby the cycle is repeated.

#### Claims

1. A product for the treatment of menopausal or post-menopausal disorders comprising, in combination, progestogen and estrogen in a form in which progestogen is to be administered uninterruptedly in a daily dosage equivalent to orally administered laevo-norgestrel in an amount of from 0.025mg to 0.075mg and estrogen is to be administered by cyclical administration in an amount in a daily dosage equivalent to orally administered estradiol in an amount of from 0.5mg up to 2.0mg.
2. A product according to claim 1 in which the progestogen is administered in a daily dosage equivalent to 0.025 mg to 0.050mg orally administered laevo-norgestrel and the estrogen is administered in a daily dosage equivalent to 0.5mg to 1.0mg orally administered estradiol.
3. A product according to claim 1 which comprises a plurality of unit dosages for oral administration in which estrogen is administered using a dose regimen comprising:
  - i) administering estrogen continuously for a period of time between 20 and 120 days in a daily dosage equivalent to orally administered estradiol in an amount of from 0.5mg up to 2.0mg followed by
  - ii) omitting to administer estrogen for a period of time between 3 and 7 days.
4. A product according to claim 3 in which the product is a multipreparation pack and also comprises instructions for use of the preparation in the defined manner.

5. A product according to claim 3 or 4, wherein the estrogen is administered in a daily dosage equivalent to from 0.5mg to 1.0mg orally administered estradiol.
6. A product for the treatment of menopausal or post-menopausal disorders comprising, in combination, progestogen and estrogen in a form in which progestogen is to be administered uninterruptedly in a daily dosage equivalent to orally administered laevo-norgestrel in an amount of from 0.025mg to 0.075mg and estrogen is to be administered uninterruptedly in an amount in a daily dosage equivalent to orally administered estradiol in an amount of from 0.5mg up to 2.0mg, with the proviso that where estradiol valerate and norethisterone acetate are to be administered, the maximum daily dosage of said estradiol valerate is equivalent to orally administered estradiol in an amount of 1.0mg.
7. A product according to any of claims 1, 3, 4 or 6 in which the estrogen is selected from the following compounds in daily dosages from amounts equivalent to orally administered dosages of the stated minima up to amounts equivalent to orally administered dosages of the stated maxima (in mg):

	Dosage Minimum	Dosage Maximum
Estradiol	0.500	2
Estradiol-17 $\beta$	0.500	2
Estradiol valerate	0.500	2
Conjugated equine estrogens	0.300	2.5
Estrone	0.300	2.5
Piperazine estrone sulphate (estropipate)	0.250	2.5
Estriol	0.050	0.5
Estriol succinate	0.050	0.5
Polyestriol phosphate	0.050	0.5
Synthetic estrogens (steroids)		
Ethinyl estradiol	0.005	0.020
Mestranol	0.005	0.040
Quinestranol	0.005	0.030

8. A product according to claim 1 or any of claims 3-7 in which the progestogen is selected from the following compounds in daily dosages from amounts equivalent to orally administered dosages of the stated minima up to amounts equivalent to orally administered dosages of the stated maxima (in mg):

	Dosage Minimum	Dosage Maximum
Laevo-norgestrel	0.025	0.075
dl-norgestrel	0.050	0.150
Norethindrone (norethisterone)	0.15	1.0
Norethindrone (norethisterone) acetate	0.10	1.0
Ethinodiol diacetate	0.10	1.0
Dydrogesterone	5	30
Medroxyprogesterone acetate	1	15
Norethynodrel	0.200	5
Allylestrenol	1	10
Lynoeestrenol	0.100	2
Quingestanol acetate	0.050	1
Medrogestone	1	10
Norgestrienone	0.020	0.2
Dimethisterone	0.500	15
Ethisterone	1	25
Cyproterone acetate	0.100	10
Chlormadinone acetate	0.100	1
Megestrol acetate	0.100	10

9. A product according to claim 6 in which the progestogen is administered uninterruptedly in a daily dosage equivalent to orally administered laevo-norgestrel in an amount of from 0.025mg to 0.075mg and the estrogen is administered uninterruptedly in a daily dosage equivalent to orally administered estradiol in an amount of from 0.5mg up to 1.0mg.
10. A product according to any of claims 1-9 in which the estrogen is selected from the following compounds in daily dosages from amounts equivalent to orally administered dosages of the stated minima up to amounts equivalent to orally administered dosages of the stated maxima (in mg):

	Dosage Minimum	Dosage Maximum
Estradiol	0.500	1
Estradiol-17 $\beta$	0.500	1
Estradiol valerate	0.500	1
Conjugated equine estrogens	0.300	0.6
Estrone	0.300	0.6
Piperazine estrone sulphate (estropipate)	0.250	0.5
Estriol	0.050	0.100
Estriol succinate	0.050	0.100
Polyestriol phosphate	0.050	0.100
Synthetic estrogens (steroids)		
Ethinyl estradiol	0.005	0.010
Mestranol	0.005	0.015
Quinestranol	0.005	0.010

11. A product according to any of claims 1-10 in which the progestogen is selected from the following compounds in daily dosages from amounts equivalent to orally administered dosages of the stated minima up to amounts equivalent to orally administered dosages of the stated maxima (in mg):

	Dosage Minimum	Dosage Maximum
Laevo-norgestrel	0.025	0.050
dl-norgestrel	0.050	0.100
Norethindrone (norethisterone)	0.15	0.30
Norethindrone (norethisterone) acetate	0.10	0.20
Ethinodiol diacetate	0.10	0.30
Dydrogesterone	5	10
Medroxyprogesterone acetate	1	2.5
Norethynodrel	0.200	1
Allylestrenol	1	2
Lynoestrenol	0.100	0.200
Quingestanol acetate	0.050	0.200
Medrogestone	1	2
Norgestrienone	0.020	0.050
Dimethisterone	0.500	1
Ethisterone	1	2.5
Cyproterone acetate	0.100	0.5
Chlormadinone acetate	0.100	0.300
Megestrol acetate	0.100	1

12. A product according to claim 7 or claim 10 in which the estrogen is selected from estradiol, estradiol-17 $\beta$ , estradiol valerate, conjugated equine estrogens, estrone, piperazine estrone sulphate (estropipate), ethinyl estradiol, mestranol and quinestranol.

13. A product according to claim 8 or claim 11 in which the progestogen is selected from Laevo-norgestrel, dl-norgestrel, norethindrone (norethisterone), norethindrone (norethisterone) acetate, ethinodiol diacetate, dydrogesterone, medroxyprogesterone acetate, norethynodrel, allylestrenol, lynoestrenol, quingestanol acetate, medrogestone, norgestrienone, dimethisterone, ethisterone and cyproterone acetate.

14. A product according to any preceding claim in which the estrogen is selected from the following compounds in a form to be administered in daily dosages equivalent to orally administered compound in about the stated amount:

	Daily Dosage (mg)
Estradiol	1
Estradiol-17 $\beta$	1
Estradiol valerate	1
Conjugated equine estrogens	0.600
Estrone	0.600
Piperazine estrone sulphate (estropipate)	0.500
Ethinyl estradiol	0.010
Mestranol	0.015
Quinestranol	0.010

15. A product according to any preceding claim in which the progestogen is selected from the following compounds in a form to be administered in daily dosages equivalent to orally administered compound in about the stated amount:

	Daily Dosage (mg)
Laevo-norgestrel	0.050
dl-norgestrel	0.100
Norethindrone (norethisterone)	0.30
Norethindrone (norethisterone) acetate	0.20
Ethinodiol diacetate	0.30
Dydrogesterone	10
Medroxyprogesterone acetate	2.5
Norethynodrel	1
Allylestrenol	2
Lynoeestrenol	0.200
Quingestanol acetate	0.200
Medrogestone	2
Norgestrienone	0.050
Dimethisterone	1
Ethisterone	2.5

16. A product according to any preceding claim in which the estrogen and progestogen are selected from the following combinations:

Estradiol/Laevo-norgestrel  
 Estradiol-17 $\beta$ /Laevo-norgestrel  
 Estradiol valerate/Laevo-norgestrel  
 Conjugated equine estrogens/Laevo-norgestrel

Estradiol/dl-norgestrel  
 Estradiol-17 $\beta$ /dl-norgestrel  
 Estradiol valerate/dl-norgestrel  
 Conjugated equine estrogens/dl-norgestrel  
 5 Estradiol/Norethindrone (norethisterone)  
 Estradiol-17 $\beta$ /Norethindrone (norethisterone)  
 Estradiol valerate/Norethindrone (norethisterone)  
 Conjugated equine estrogens/Norethindrone (norethisterone)  
 Estradiol/Norethindrone (norethisterone) acetate  
 10 Estradiol-17 $\beta$ /Norethindrone (norethisterone) acetate  
 Estradiol valerate/Norethindrone (norethisterone) acetate  
 Conjugated equine estrogen/Norethindrone (norethisterone) acetate  
 Estradiol/Medroxyprogesterone acetate  
 Estradiol-17 $\beta$ /Medroxyprogesterone acetate  
 15 Estradiol valerate/Medroxyprogesterone acetate  
 Conjugated equine estrogen/Medroxyprogesterone acetate

17. A product according to any preceding claim in which the estrogen is 17 $\beta$ -estradiol and the progestogen is selected from dl-norgestrel and laevo-norgestrel.

18. The product of claim 17 wherein said estrogen is 17 $\beta$ -estradiol and said progestogen is dl-norgestrel or laevo-norgestrel, the daily dosage level of said 17 $\beta$ -estradiol being about 1 mg, the daily dosage level of said dl-norgestrel (where present) being about 100 micrograms, and the daily dosage of said laevo-norgestrel (where present) being about 50 micrograms.

19. A product for the treatment of menopausal or post-menopausal disorders comprising in combination, progestogen and estrogen in which progestogen is to be administered uninterruptedly in a daily dosage equivalent to orally administered laevo-norgestrel in an amount up to 0.075mg and estrogen is to be administered either uninterruptedly or cyclically in an amount in a daily dosage equivalent to orally administered estradiol in an amount up to 2.0mg and at least the progestogen is in the form of a slow release composition suitable for implanting or injecting intramuscularly.

20. A product according to claim 19 in which the progestogen is selected from the following compounds in compositions comprising the compound in the amount indicated and being intended for replacements after the periods indicated:

Progestogen implants	Total Quantity (mg)			
	Period	Preferred	Minimum	Maximum
Laevo-norgestrel	every 2-5 yr.	50	25	100
dl-norgestrel	every 2-5 yr.	100	50	200
Norgestrienone	every 1-2 yr.	100	25	200
45 Norethindrone acetate	every 2-4 mon.	100	25	200
Intramuscular progestogen depots				
Medroxyprogesterone acetate	every 3 mon.	150	50	500
50 Norethindrone enanthate	every 3 mon.	50	20	400
Gestronol hexanoate	every 3 mon.	100	50	400
Algestone acetephenide	monthly	50	20	300
Hydroxyprogesterone hexanoate	weekly	100	50	250
55 Hydroxyprogesterone caproate	bi-weekly	100	50	250



21. A product according to claim 19 or claim 20 in which the estrogen is selected from the following compounds in daily dosages from amounts equivalent to orally administered dosages of the stated minima up to amounts equivalent to orally administered dosages of the stated maxima (in mg):

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	Dosage Minimum	Preferred Maximum	Maximum
Estradiol	0.500	1	2
Estradiol-17 $\beta$	0.500	1	2
Estradiol valerate	0.500	1	2
Conjugated equine estrogens	0.300	0.600	2.5
Estrone	0.300	0.600	2.5
Piperazine estrone sulphate (estropipate)	0.250	0.500	2.5
Estriol	0.050	0.100	0.500
Estriol succinate	0.050	0.100	0.500
Polyestriol phosphate	0.050	0.100	0.500
Synthetic estrogens (steroids)			
Ethinyl estradiol	0.005	0.010	0.020
Mestranol	0.005	0.015	0.040
Quinestranol	0.005	0.010	0.030

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22. A product according to claim 21 in which the estrogen is selected from estradiol, estradiol-17 $\beta$ , estradiol valerate, conjugated equine estrogens, estrone, piperazine estrone sulphate (estropipate), ethinyl estradiol, mestranol and quinestranol.

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23. A product according to any of claims 19 to 22 in which the estrogen and progestogen are in a form in which both the progestogen and the estrogen are to be administered continuously and uninterruptedly.

24. A product according to any of claims 19 to 23 in which both the progestogen and estrogen are in the form of a slow release composition suitable for implanting or injecting intramuscularly.

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25. A product according to any of claims 1 to 16 or 19 to 24 in which the estrogen is conjugated equine estrogens and the progestogen is medroxyprogesterone acetate.

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26. A product according to any of claims 19 to 24 in which said composition or compositions comprise estrogen selected from estradiol, estradiol valerate and estradiol-17 $\beta$  in an amount in the range 20 to 100mg, preferably about 100mg.

27. Use of estrogen in the manufacture of a product for the treatment of menopausal or post menopausal disorders in a woman characterized in that the product is as defined in any preceding claim.

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28. Use of progestogen in the manufacture of a product for the treatment of menopausal or post-menopausal disorders in a woman characterized in that the product is as defined in any of claims 1 to 26.

#### Patentansprüche

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1. Produkt zur Behandlung von Störungen in der Menopause oder Postmenopause, umfassend Progestogen und Estrogen in Kombination in einer Form, in der Progestogen ununterbrochen in einer Tagesdosis zu verabreichen ist, die oral verabreichtem Laevo-Norgestrel in einer Menge von 0,025 mg bis 0,075 mg äquivalent ist, und Estrogen durch cyclische Verabreichung in einer Menge in einer Tagesdosis zu verabreichen ist, die oral verabreichtem

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Estradiol in einer Menge von 0,5 mg bis zu 2,0 mg äquivalent ist.

2. Produkt nach Anspruch 1, worin das Progestogen in einer Tagesdosis verabreicht wird, die 0,025 mg bis 0,050 mg oral verabreichtem Laevo-Norgestrel äquivalent ist, und das Estrogen in einer Tagesdosis verabreicht wird, die 0,5 mg bis 1,0 mg oral verabreichtem Estradiol äquivalent ist.
3. Produkt nach Anspruch 1, welches eine Vielzahl von Einheitsdosen für die orale Verabreichung umfaßt, wobei Estrogen unter Einhaltung eines Dosisplans verabreicht wird, welcher umfaßt:
  - i) kontinuierliche Verabreichung von Estrogen für einen Zeitraum zwischen 20 und 120 Tagen in einer Tagesdosis, die oral verabreichtem Estradiol in einer Menge von 0,5 mg bis 2,0 mg äquivalent ist, gefolgt von
  - ii) Unterlassen der Estrogenverabreichung für einen Zeitraum zwischen 3 und 7 Tagen.
4. Produkt nach Anspruch 3, worin das Produkt eine Multipräparatpackung ist und auch Anweisungen zur Anwendung des Präparats in der definierten Art und Weise umfaßt.
5. Produkt nach Anspruch 3 oder 4, worin das Estrogen in einer Tagesdosis verabreicht wird, die 0,5 mg bis 1,0 mg oral verabreichtem Estradiol äquivalent ist.
6. Produkt zur Behandlung von Störungen in der Menopause oder Postmenopause, umfassend Progestogen und Estrogen in Kombination in einer Form, in der Progestogen ununterbrochen in einer Tagesdosis zu verabreichen ist, die oral verabreichtem Laevo-Norgestrel in einer Menge von 0,025 mg bis 0,075 mg äquivalent ist, und Estrogen ununterbrochen in einer Menge in einer Tagesdosis zu verabreichen ist, die oral verabreichtem Estradiol in einer Menge von 0,5 mg bis zu 2,0 mg äquivalent ist, mit der Maßgabe, daß wenn Estradiolvalerat und Norethisteronacetat zu verabreichen sind, die tägliche Maximaldosis des Estradiolvalerats oral verabreichtem Estradiol in einer Menge von 1,0 mg äquivalent ist.
7. Produkt nach irgendeinem der Ansprüche 1, 3, 4 oder 6, worin das Estrogen ausgewählt ist aus den folgenden Verbindungen in Tagesdosen von Mengen, die oral verabreichten Dosen der angegebenen Minima äquivalent sind, bis zu Mengen, die oral verabreichten Dosen der angegebenen Maxima (in mg) äquivalent sind:

	Minimaldosis	Maximaldosis
Estradiol	0,500	2
Estradiol-17β	0,500	2
Estradiolvalerat	0,500	2
Konjugierte Pferdeestrogene	0,300	2,5
Estron	0,300	2,5
Piperazinestrone-sulfat (Estropipat)	0,250	2,5
Estriol	0,050	0,5
Estriolsuccinat	0,050	0,5
Polyestriolphosphat	0,050	0,5
Synthetische Estrogene (Steroide)		
Ethinylestradiol	0,005	0,020
Mestranol	0,005	0,040
Quinestranol	0,005	0,030

8. Produkt nach Anspruch 1 oder irgendeinem der Ansprüche 3 - 7, worin das Progestogen ausgewählt ist aus den folgenden Verbindungen von Mengen, die oral verabreichten Dosen der angegebenen Minima äquivalent sind, bis zu Mengen, die oral verabreichten Dosen der angegebenen Maxima (in mg) äquivalent sind:

	Minimaldosis	Maximaldosis
Laevo-Norgestrel	0,025	0,075
dl-Norgestrel	0,050	0,150
Norethindron (Norethisteron)	0,15	1,0
Norethindron (Norethisteron)acetat	0,10	1,0
Ethinodioldiacetat	0,10	1,0
Dydrogesteron	5	30
Medroxyprogesteronacetat	1	15
Norethynodrel	0,200	5
Allylestrenol	1	10
Lynöestrenol	0,100	2
Quingestanolacetat	0,050	1
Medrogeston	1	10
Norgestrienon	0,020	0,2
Dimethisteron	0,500	15
Ethisteron	1	25
Cyproteronacetat	0,100	10
Chlormadinonacetat	0,100	1
Megestrolacetat	0,100	10

9. Produkt nach Anspruch 6, worin das Progestogen ununterbrochen in einer Tagesdosis verabreicht wird, die oral verabreichtem Laevo-Norgestrel in einer Menge von 0,025 mg bis 0,075 mg äquivalent ist, und das Estrogen ununterbrochen in einer Tagesdosis verabreicht wird, die oral verabreichtem Estradiol in einer Menge von 0,5 mg bis zu 1,0 mg äquivalent ist.
10. Produkt nach irgendeinem der Ansprüche 1 - 9, worin das Estrogen ausgewählt ist aus den folgenden Verbindungen in Tagesdosen von Mengen, die oral verabreichten Dosen der angegebenen Minima äquivalent sind, bis zu Mengen, die oral verabreichten Dosen der angegebenen Maxima (in mg) äquivalent sind:

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	Minimaldosis	Maximaldosis
Estradiol	0,500	1
Estradiol-17 $\beta$	0,500	1
Estradiolvalerat	0,500	1
Konjugierte Pferdeestrogene	0,300	0,6
Estron	0,300	0,6
Piperazinestronsulfat (Estropipat)	0,250	0,5
Estriol	0,050	0,100
Estriolsuccinat	0,050	0,100
Polyestriolphosphat	0,050	0,100
Synthetische Estrogene (Steroide)		
Ethinylestradiol	0,005	0,010
Mestranol	0,005	0,015
Quinestranol	0,005	0,010

11. Produkt nach irgendeinem der Ansprüche 1 - 10, worin das Progestogen ausgewählt ist aus den folgenden Verbindungen in Tagesdosen von Mengen, die oral verabreichten Dosen der angegebenen Minima äquivalent sind, bis zu Mengen, die oral verabreichten Dosen der angegebenen Maxima (in mg) äquivalent sind:

		Minimaldosis	Maximaldosis
5	Laevo-Norgestrel	0,025	0,050
	dl-Norgestrel	0,050	0,100
	Norethindron (Norethisteron)	0,15	0,30
	Norethindron		
10	(Norethisteron)acetat	0,10	0,20
	Ethinodioldiacetat	0,10	0,30
	Dydrogesteron	5	10
15	Medroxyprogesteronacetat	1	2,5
	Norethynodrel	0,200	1
	Allylestrenol	1	2
	Lynoestrenol	0,100	0,200
20	Quingestanolacetat	0,050	0,200
	Medrogeston	1	2
	Norgestrienon	0,020	0,050
25	Dimethisteron	0,500	1
	Ethisteron	1	2,5
	Cyproteronacetat	0,100	0,5
	Chlormadinonacetat	0,100	0,300
30	Megestrolacetat	0,100	1

- 35 12. Produkt nach Anspruch 7 oder Anspruch 10, worin das Estrogen aus Estradiol, Estradiol-17 $\beta$ , Estradiolvalerat, konjugierten Pferdeestrogenen, Estron, Piparazinestronsulfat (Estropipat), Ethinylestradiol, Mestranol und Quinestranol ausgewählt ist.
- 40 13. Produkt nach Anspruch 8 oder Anspruch 11, worin das Progestogen aus Laevo-Norgestrel, dl-Norgestrel, Norethindron (Norethisteron), Norethindron(Norethisteron)acetat, Ethynodioldiacetat, Dydrogesteron, Medroxyprogesteronacetat, Norethynodrel, Allylestrenol, Lynoestrenol, Quingestanolacetat, Medrogeston, Norgestrienon, Dimethisteron, Ethisteron und Cyproteronacetat ausgewählt ist.
- 45 14. Produkt nach irgendeinem der vorhergehenden Ansprüche, worin das Estrogen ausgewählt ist aus den folgenden Verbindungen in einer Form, um in Tagesdosen verabreicht zu werden, die oral verabreichter Verbindung in etwa der angegebenen Menge äquivalent sind:

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	Tagesdosis (mg)
Estradiol	1
Estradiol-17 $\beta$	1
Estradiolvalerat	1
Konjugierte Pferdeestrogene	0,600
Estron	0,600
Piperazinestronsulfat (Estropipat)	0,500
Ethinylestradiol	0,010
Mestranol	0,015
Quinestranol	0,010

15. Produkt nach irgendeinem der vorhergehenden Ansprüche, worin das Progestogen ausgewählt ist aus den folgenden Verbindungen in einer Form, um in Tagesdosen verabreicht zu werden, die oral verabreichter Verbindung in etwa der angegebenen Menge äquivalent sind:

	Tagesdosis (mg)
Laevo-Norgestrel	0,050
di-Norgestrel	0,100
Norethindron (Norethisteron)	0,30
Norethindron(Norethisteron)acetat	0,20
Ethinodioldiacetat	0,30
Dydrogesteron	10
Medroxyprogesteronacetat	2,5
Norethynodrel	1
Allylestrenol	2
Lynoestrenol	0,200
Quingestanolacetat	0,200
Medrogeston	2
Norgestrienon	0,050
Dimethisteron	1
Ethisteron	2,5
Cyproteronacetat	0,500

16. Produkt nach irgendeinem der vorhergehenden Ansprüche, worin das Estrogen und Progestogen aus den folgenden Kombinationen ausgewählt sind:  
 Estradiol/Laevo-Norgestrel  
 Estradiol-17 $\beta$ /Laevo-Norgestrel

Estradiolvalerat/Laevo-Norgestrel  
 Konjugierte Pferdeestrogene/Laevo-Norgestrel  
 Estradiol/dl-Norgestrel  
 Estradiol-17 $\beta$ /dl-Norgestrel  
 Estradiolvalerat/dl-Norgestrel  
 Konjugierte Pferdeestrogene/dl-Norgestrel  
 Estradiol/Norethindron (Norethisteron)  
 Estradiol-17 $\beta$ /Norethindron (Norethisteron)  
 Estradiolvalerat/Norethindron (Norethisteron)  
 Konjugierte Pferdeestrogene/Norethindron (Norethisteron)  
 Estradiol/Norethindron(Norethisteron)acetat  
 Estradiol-17 $\beta$ /Norethindron(Norethisteron)acetat  
 Estradiolvalerat/Norethindron(Norethisteron)acetat  
 Konjugiertes Pferdeestrogen/Norethindron(Norethisteron)acetat  
 Estradiol/Medroxyprogesteronacetat  
 Estradiol-17 $\beta$ /Medroxyprogesteronacetat  
 Estradiolvalerat/Medroxyprogesteronacetat  
 Konjugiertes Pferdeestrogen/Medroxyprogesteronacetat

17. Produkt nach irgendeinem der vorhergehenden Ansprüche, worin das Estrogen 17 $\beta$ -Estradiol ist und das Progestogen aus dl-Norgestrel und Laevo-Norgestrel ausgewählt ist.
18. Produkt nach Anspruch 17, worin das Estrogen 17 $\beta$ -Estradiol ist und das Progestogen dl-Norgestrel oder Laevo-Norgestrel ist, wobei das Tagesdosisniveau des 17 $\beta$ -Estradiols etwa 1 mg beträgt, das Tagesdosisniveau des dl-Norgestrels (falls vorhanden) etwa 100 Mikrogramm beträgt und das Tagesdosisniveau des Laevo-Norgestrels (falls vorhanden) etwa 50 Mikrogramm beträgt.
19. Produkt zur Behandlung von Störungen in der Menopause oder Postmenopause, umfassend Progestogen und Estrogen in Kombination, wobei Progestogen ununterbrochen in einer Tagesdosis zu verabreichen ist, die oral verabreichtem Laevo-Norgestrel in einer Menge bis zu 0,075 mg äquivalent ist, und Estrogen ununterbrochen oder cyclisch in einer Menge in einer Tagesdosis zu verabreichen ist, die oral verabreichtem Estradiol in einer Menge bis zu 2,0 mg äquivalent ist, und mindestens das Progestogen in Form einer Zusammensetzung zur langsamen Freisetzung vorliegt, die zur Implantation oder intramuskulären Injektion geeignet ist.
20. Produkt nach Anspruch 19, worin das Progestogen ausgewählt ist aus den folgenden Verbindungen in Zusammensetzungen, welche die Verbindung in der angegebenen Menge umfassen und nach den angegebenen Zeiträumen ersetzt werden sollen:

Progestogen-Implantate	Gesamtmenge (mg)			
	Zeitraum	Bevorzugt	Minimum	Maximum
Laevo-Norgestrel	alle 2-5 Jahre	50	25	100
dl-Norgestrel	alle 2-5 Jahre	100	50	200
Norgestrienon	alle 1-2 Jahre	100	25	200
Norethindronacetat	alle 2-4 Mon.	100	25	200
Intramuskuläre Progestogen-Depots				
Medroxyprogesteronacetat	alle 3 Monate	150	50	500
Norethindronenanthat	alle 3 Monate	50	20	400
Gestronolhexanoat	alle 3 Monate	100	50	400
Algestonacetphenid	monatlich	50	20	300
Hydroxyprogesteronhexanoat	wöchentlich	100	50	250
Hydroxyprogesteroncaproat	zweiwöchentl.	100	50	250

21. Produkt nach Anspruch 19 oder Anspruch 20, worin das Estrogen ausgewählt ist aus den folgenden Verbindungen in Tagesdosen von Mengen, die oral verabreichten Dosen der angegebenen Minima äquivalent sind, bis zu Mengen, die oral verabreichten Dosen der angegebenen Maxima (in mg) äquivalent sind:

	Dosierungs-Minimum	Bevorzugtes Maximum	Maximum
Estradiol	0,500	1	2
Estradiol-17 $\beta$	0,500	1	2
Estradiolvalerat	0,500	1	2
Konjugierte Pferdeestrogene	0,300	0,600	2,5
Estron	0,300	0,600	2,5
Piperazinestronsulfat (Estropipat)	0,250	0,500	2,5
Estriol	0,050	0,100	0,500
Estriolsuccinat	0,050	0,100	0,500
Polyestriolphosphat	0,050	0,100	0,500
Synthetische Estrogene (Steroide)			
Ethinylestradiol	0,005	0,010	0,020
Mestranol	0,005	0,015	0,040
Quinestranol	0,005	0,010	0,030

22. Produkt nach Anspruch 21, worin das Estrogen ausgewählt ist aus Estradiol, Estradiol-17 $\beta$ , Estradiolvalerat, konjugierten Pferdeestrogenen, Estron, Piperazinestronsulfat (Estropipat), Ethinylestradiol, Mestranol und Quinestranol.

23. Produkt nach irgendeinem der Ansprüche 19 bis 22, worin das Estrogen und Progestogen in einer Form vorliegen, in der sowohl das Progestogen als auch das Estrogen kontinuierlich und ununterbrochen verabreicht werden.

24. Produkt nach irgendeinem der Ansprüche 19 bis 23, worin das Progestogen und Estrogen beide in Form einer Zusammensetzung zur langsamen Freisetzung vorliegen, die zur Implantation oder intramuskulären Injektion geeignet ist.

25. Produkt nach irgendeinem der Ansprüche 1 bis 16 oder 19 bis 24, worin das Estrogen konjugierte Pferdeestrogene darstellt und das Progestogen Medroxyprogesteronacetat darstellt.

26. Produkt nach irgendeinem der Ansprüche 19 bis 24, worin die Zusammensetzung oder Zusammensetzungen Estrogen umfaßt bzw. umfassen, das aus Estradiol, Estradiolvalerat und Estradiol-17 $\beta$  in einer Menge im Bereich von 20 bis 100 mg, vorzugsweise etwa 100 mg, ausgewählt ist.

27. Verwendung von Estrogen zur Herstellung eines Produkts zur Behandlung von Störungen in der Menopause oder Postmenopause einer Frau, dadurch gekennzeichnet, daß das Produkt wie in irgendeinem der vorhergehenden Ansprüche definiert ist.

28. Verwendung von Progestogen zur Herstellung eines Produkts zur Behandlung von Störungen in der Menopause oder Postmenopause einer Frau, dadurch gekennzeichnet, daß das Produkt wie in irgendeinem der Ansprüche 1 bis 26 definiert ist.



## Revendications

1. Produit destiné au traitement des troubles ménopausiques ou postménopausiques, comprenant en association, un progestatif et un oestrogène sous une forme dans laquelle le progestatif doit être administré de façon ininterrompue à une posologie quotidienne équivalente à l'administration orale de lévonorgestrel en une quantité de 0,025 mg à 0,075 mg et l'oestrogène doit être administré par administration cyclique en une quantité à une posologie quotidienne équivalente à l'administration orale d'estradiol en une quantité de 0,5 mg à 2,0 mg.
2. Produit selon la revendication 1, dans lequel le progestatif est administré à une posologie quotidienne équivalente à 0,025 mg à 0,050 mg de lévonorgestrel administré par voie orale et l'oestrogène est administré à une posologie quotidienne équivalente à 0,5 mg à 1,0 mg d'estradiol administré par voie orale.
3. Produit selon la revendication 1, lequel comprend une pluralité de présentations unitaires destinées à l'administration orale, dans lequel l'oestrogène est administré selon un régime posologique comprenant :
  - i) l'administration continue de l'oestrogène pendant une durée comprise entre 20 et 120 jours à une posologie quotidienne équivalente à l'administration orale d'estradiol en une quantité de 0,5 mg à 2,0 mg, suivie de
  - ii) la suppression de l'administration de l'oestrogène pendant une durée comprise entre 3 et 7 jours.
4. Produit selon la revendication 3, le produit étant une présentation multipréparation et comprenant également le mode d'emploi de la préparation d'une manière définie.
5. Produit selon la revendication 3 ou 4, dans lequel l'oestrogène est administré à une posologie quotidienne équivalente à 0,5 mg à 1,0 mg d'estradiol administré par voie orale.
6. Produit destiné au traitement des troubles ménopausiques ou postménopausiques, comprenant, en association, un progestatif et un oestrogène sous une forme dans laquelle le progestatif doit être administré de façon ininterrompue à une posologie quotidienne équivalente à l'administration orale de lévonorgestrel en une quantité comprise entre 0,025 mg et 0,075 mg et l'oestrogène doit être administré de façon ininterrompue en une quantité à une posologie quotidienne équivalente à l'administration orale d'estradiol en une quantité comprise entre 0,5 mg et 2,0 mg, à la condition que, lorsqu'on doit administrer du valérate d'estradiol ou de l'acétate de noréthistérone, la posologie quotidienne maximale dudit valérate d'estradiol soit équivalente à l'administration orale d'estradiol en une quantité de 1,0 mg.
7. Produit selon l'une quelconque des revendications 1, 3, 4 ou 6, dans lequel l'oestrogène est sélectionné parmi les composés suivants à des posologies quotidiennes allant de quantités équivalentes à l'administration orale des posologies aux minima indiqués à des quantités équivalentes à l'administration orale des posologies aux maxima indiqués (en mg):

	Posologie minimale	Posologie maximale
Estradiol	0,500	2
Estradiol-17 $\beta$	0,500	2
Valérate d'estradiol	0,500	2
Oestrogènes équins conjugués	0,300	2,5
Estrone	0,300	2,5
Sulfate d'estrone-pipérazine (estropipate)	0,250	2,5
Estriol	0,050	0,5
Succinate d'estriol	0,050	0,5
Phosphate de polyestriol	0,050	0,5
Oestrogènes de synthèse (phénylstéroïdes)		
Ethinylestradiol	0,005	0,020
Mestranol	0,005	0,040
Quinestranol	0,005	0,030

8. Procédé selon la revendication 1 ou selon l'une quelconque des revendications 3 à 7, dans lequel le progestatif est sélectionné parmi les composés suivants à des posologies quotidiennes allant de quantités équivalentes à l'administration orale des posologies aux minima indiquées à des quantités équivalentes à l'administration orale des posologies aux maxima indiquées (en mg):

		Posologie minimale	Posologie maximale
5	Lévonorgestrel	0,025	0,075
	di-norgestrel	0,050	0,150
	Noréthindrone (noréthistérone)	0,15	1,0
10	Acétate de noréthindrone (noréthistérone)	0,10	1,0
	Diacétate d'éthinodiol	0,10	1,0
	Dydrogestérone	5	30
	Acétate de médroxyprogesterone	1	15
15	Noréthynodrel	0,200	5
	Allylestrénol	1	10
	Lynestrénol	0,100	2
20	Acétate de quingestanol	0,050	1
	Médrogestone	1	10
	Norgestriénone	0,020	0,2
	Diméthistérone	0,500	15
25	Ethistérone	1	25
	Acétate de cyprotérone	0,100	10
	Acétate de chlormadinone	0,100	1
30	Acétate de mégestrol	0,100	10

- 35 9. Produit selon la revendication 6, dans lequel le progestatif est administré de façon ininterrompue à une posologie quotidienne équivalente à l'administration orale de lévonorgestrel en une quantité comprise entre 0,025 mg et 0,075 mg et l'oestrogène est administré de façon ininterrompue à une posologie quotidienne équivalente à l'administration orale d'estradiol en une quantité comprise entre 0,5 mg et 1,0 mg.
- 40 10. Produit selon l'une quelconque des revendications 1 à 9, dans lequel l'oestrogène est sélectionné parmi les composés suivants à des posologies quotidiennes allant de quantités équivalentes à l'administration orale des posologies aux minima indiquées à des quantités équivalentes à l'administration orale des posologies aux maxima indiqués (en mg):

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	Posologie minimale	Posologie maximale
Estradiol	0,500	1
Estradiol-17 $\beta$	0,500	1
Valérate d'estradiol	0,500	1
Oestrogènes équins conjugués	0,300	0,6
Estrone	0,300	0,6
Sulfate d'estrone-pipérazine (estropipate)	0,250	0,5
Estriol	0,050	0,100
Succinate d'estriol	0,050	0,100
Phosphate de polyestriol	0,050	0,100
Oestrogènes de synthèse (phénylistéroïdes)		
Ethinylestradiol	0,005	0,010
Mestranol	0,005	0,015
Quinestranol	0,005	0,010

11. Produit selon l'une quelconque des revendications 1 à 10, dans lequel le progestatif est sélectionné parmi les composés suivants à des posologies quotidiennes allant de quantités équivalentes à l'administration orale de posologies aux minima indiquées à des quantités équivalentes à l'administration orale des posologies aux maxima indiqués (en mg):

	Posologie minimale	Posologie maximale
5 Lévonorgestrel	0,025	0,050
di-norgestrel	0,050	0,100
Noréthindrone (noréthistérone)	0,15	0,30
10 Acétate de noréthindrone (noréthistérone)	0,10	0,20
Diacétate d'éthynodiol	0,10	0,30
Dydrogestérone	5	10
Acétate de médroxyprogestérone	1	2,5
15 Noréthynodrel	0,200	1
Allylestrénol	1	2
Lynestrénol	0,100	0,200
20 Acétate de quingestanol	0,050	0,200
Médrogestone	1	2
Norgestriénone	0,020	0,050
Diméthistérone	0,500	1
25 Ethistérone	1	2,5
Acétate de cyprotérone	0,100	0,5
Acétate de chlormadinone	0,100	0,300
30 Acétate de mégestrol	0,100	1

- 35 12. Produit selon la revendication 7 ou la revendication 10, dans lequel l'oestrogène est sélectionné parmi l'estradiol, l'estradiol-17 $\beta$ , le valérate d'estradiol, les oestrogènes équins conjugués, l'estrone, le sulfate d'estronepipérazine (estropipate), l'éthinylestradiol, le mestranol et le quingestanol.
- 40 13. Produit selon la revendication 8 ou la revendication 11, dans lequel le progestatif est sélectionné parmi le lévonorgestrel, le di-norgestrel, la noréthindrone (noréthistérone), l'acétate de noréthindrone (noréthistérone), le diacétate d'éthynodiol, la dydrogestérone, l'acétate de médroxyprogestérone, le noréthynodrel, l'allylestrénol, le lynestrénol, l'acétate de quingestanol, la médrogestone, la norgestriénone, la diméthistérone, l'éthistérone et l'acétate de cyprotérone.
- 45 14. Produit selon l'une quelconque des revendications précédentes, dans lequel l'oestrogène est sélectionné parmi les composés suivants sous une forme à administrer à des posologies quotidiennes équivalentes à l'administration orale du composé à approximativement la quantité mentionnée :

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	Posologie quotidienne (mg)
Estradiol	1
Estradiol-17 $\beta$	1
Valérate d'estradiol	1
Oestrogènes équins conjugués	0,600
Estrone	0,600
Sulfate d'estrone-pipérazine (estropipate)	0,500
Ethinylestradiol	0,010
Mestranol	0,015
Quinestranol	0,010

15. Produit selon l'une quelconque des revendications précédentes, dans lequel le progestatif est sélectionné parmi les composés suivants sous une forme à administrer à des posologies quotidiennes équivalentes à l'administration orale du composé à approximativement la quantité mentionnée :

	Posologie quotidienne
Lévonorgestrel	0,050
di-norgestrel	0,100
Noréthindrone (noréthistérone)	0,30
Acétate de noréthindrone (noréthistérone)	0,20
Diacétate d'éthinodiol	0,30
Dydrogestérone	10
Acétate de médroxyprogestérone	2,5
Noréthynodrel	1
Allylestrénol	2
Lynestrénol	0,200
Acétate de quingestanol	0,200
Médrogestone	2
Norgestriénone	0,050
Diméthistérone	1
Ethistérone	2,5
Acétate de cyprotérone	0,500

16. Produit selon l'une quelconque des revendications précédentes, dans lequel l'oestrogène et le progestatif sont sélectionnés parmi les associations suivantes :
- Estradiol/lévonorgestrel
- Estradiol-17 $\beta$ /lévonorgestrel

- Valérate d'estradiol/lévonorgestrel  
Oestrogènes équins conjugués/lévonorgestrel  
Estradiol/dl-norgestrel  
Estradiol-17β/dl-norgestrel  
5 Valérate d'estradiol/dl-norgestrel  
Oestrogènes équins conjugués/dl-norgestrel  
Estradiol/noréthindrone (noréthistérone)  
Estradiol-17β/noréthindrone (noréthistérone)  
Valérate d'estradiol/noréthindrone (noréthistérone)  
10 Oestrogènes équins conjugués/noréthindrone (noréthistérone)  
Estradiol/acétate de noréthindrone (noréthistérone)  
Estradiol-17β/acétate de noréthindrone (noréthistérone)  
Valérate d'estradiol/acétate de noréthindrone (noréthistérone)  
Oestrogènes équins conjugués/acétate de noréthindrone (noréthistérone)  
15 Estradiol/acétate de médroxyprogestérone  
Estradiol-17β/acétate de médroxyprogestérone  
Valérate d'estradiol/acétate de médroxyprogestérone  
Oestrogènes équins conjugués/acétate de médroxyprogestérone
- 20 17. Produit selon l'une quelconque des revendications précédentes, dans lequel l'oestrogène est le 17β-estradiol et le progestatif est sélectionné parmi le dl-norgestrel et le lévonorgestrel.
18. Produit selon la revendication 17, dans lequel ledit oestrogène est le 17β-estradiol et ledit progestatif est le dl-norgestrel ou le lévonorgestrel, le niveau posologique quotidien dudit 17β-estradiol étant d'environ 1 mg, le niveau posologique quotidien dudit dl-norgestrel (lorsqu'il est présent) étant d'environ 100 µg et le niveau posologique quotidien dudit lévonorgestrel (lorsqu'il est présent) étant d'environ 50 µg.
- 25 19. Produit destiné au traitement des troubles ménopausiques et postménopausique, comprenant, en association, un progestatif et un oestrogène, dans lequel le progestatif doit être administré de façon ininterrompue à une posologie quotidienne équivalente à l'administration orale de lévonorgestrel en une quantité atteignant au maximum 0,075 mg et l'oestrogène doit être administré soit de façon ininterrompue soit de façon cyclique en une quantité à une posologie quotidienne équivalente à l'administration orale d'estradiol en une quantité atteignant au maximum 2,0 mg et le progestatif au moins se présente sous la forme d'une composition à libération lente convenant à l'implantation ou à l'injection intramusculaire.
- 30 20. Produit selon la revendication 19, dans lequel le progestatif est sélectionné parmi les composés suivants en compositions comprenant le composé à la quantité indiquée et dont le remplacement est prévu après les durées indiquées :

	Implants de progestatif	Quantité totale (mg)			
		Durée	Préférée	Minimale	Maximale
45	Lévonorgestrel	tous les 2 à 5 ans	50	25	100
	dl-norgestrel	tous les 2 à 5 ans	100	50	200
	Norgestriénone	tous les 1 à 2 ans	100	25	200
	Acétate de noréthindrone	tous les 2 à 4 mois	100	25	200
50	Dépôts intramusculaires de progestatif				
55	Acétate de médroxyprogestérone	tous les 3 mois	150	50	500
	Enanthate de noréthindrone	tous les 3 mois	50	20	400
	Hexanoate de gestronol	tous les 3 mois	100	50	400
	Algestone acétophénide	tous les mois	50	20	300
	Hexanoate d'hydroxyprogestérone	toutes les semaines	100	50	250
	Caproate d'hydroxyprogestérone	2 fois / semaine	100	50	250

21. Produit selon la revendication 19 ou la revendication 20, dans lequel l'oestrogène est sélectionné parmi les composés suivants à des posologies quotidiennes allant de quantités équivalentes à l'administration orale des posologies aux minima indiquées à des quantités équivalentes à l'administration orale des posologies aux maxima indiquées (en mg) :

	Posologie minimale	Maximum préféré	Maximum
Estradiol	0,500	1	2
Estradiol-17 $\beta$	0,500	1	2
Valérate d'estradiol	0,500	1	2
Oestrogènes équins conjugués	0,300	0,600	2,5
Estrone	0,300	0,600	2,5
Sulfate d'estrone-pipérazine (estropiate)	0,250	0,500	2,5
Estriol	0,050	0,100	0,500
Succinate d'estriol	0,050	0,100	0,500
Phosphate de polyestriol	0,050	0,100	0,500
Oestrogènes de synthèse (phénylsteroides)			
Ethinylestradiol	0,005	0,010	0,020
Mestranol	0,005	0,015	0,040
Quinestranol	0,005	0,010	0,030

22. Produit selon la revendication 21, dans lequel l'oestrogène est sélectionné parmi l'estradiol, l'estradiol-17 $\beta$ , le valérate d'estradiol, les estrogènes équins conjugués, l'estrone, le sulfate d'estrone-pipérazine (estropiate), l'éthinylestradiol, le mestranol et le quinestranol.
23. Produit selon l'une quelconque des revendications 19 à 22, dans lequel l'oestrogène et le progestatif se présentent sous une forme à laquelle le progestatif et l'oestrogène doivent être administrés de façon continue et ininterrompue.
24. Produit selon l'une quelconque des revendications 19 à 23, dans lequel le progestatif et l'oestrogène se présentent sous la forme d'une composition à libération lente convenant à l'implantation ou à l'injection intramusculaire.
25. Produit selon l'une quelconque des revendications 1 à 16 ou 19 à 24, dans lequel l'oestrogène est les oestrogènes équins conjugués et le progestatif est l'acétate de médroxyprogestérone.
26. Produit selon l'une quelconque des revendications 19 à 24, dans lequel ladite composition ou lesdites compositions comprennent un oestrogène sélectionné parmi l'estradiol, le valérate d'estradiol et l'estradiol-17 $\beta$  en une quantité comprise dans la plage de 20 à 100 mg, de préférence égale à environ 100 mg.
27. Utilisation d'un oestrogène pour la préparation d'un produit destiné au traitement des troubles ménopausiques ou postménopausiques chez la femme, caractérisée en ce que le produit est tel que défini dans l'une quelconque des revendications précédentes.
28. Utilisation d'un progestatif pour la préparation d'un produit destiné au traitement des troubles ménopausiques ou postménopausiques chez la femme, caractérisée en ce que le produit est tel que défini dans l'une quelconque des revendications 1 à 26.



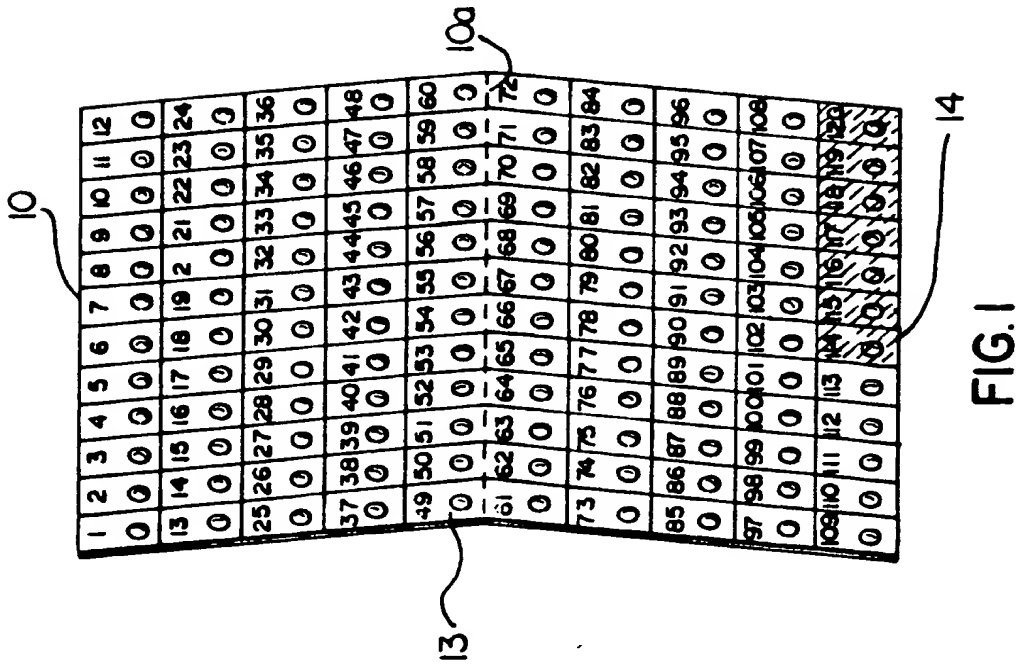


FIG. 1

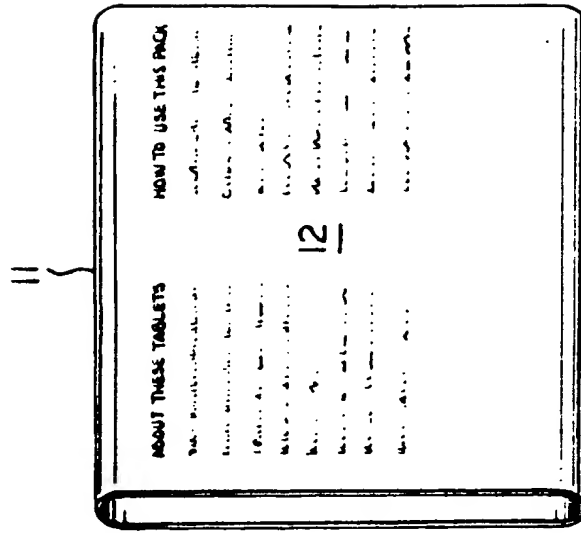


FIG. 2